2024

Efficacy of Platelet Rich Plasma Injections to Combat Chronic Tendinopathies

Rachel Kisse
University of North Dakota

Efficacy of Platelet Rich Plasma Injections to Combat Chronic Tendinopathies

By

Rachel Kisse, PA-S

Bachelor of Science, North Dakota State University, 2021

Contributing Author: Mindy Staveteig, MMS, PA-C

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2024

Table of Contents

Acknowledgements

I would like to acknowledge and thank my project advisor, Mindy Staveteig, and course director, Russ Kauffman for their continued guidance and contributions throughout this enduring project. In addition, a huge thank you is extended to Marilyn Klug for her expertise in statistics and helping me breakdown various scholarly articles. Lastly, I would like to thank my parents, family, and friends that have supported me and guided me throughout my journey to become a competent Physician Assistant. Without their support, there would have been no way I would have made it through this schooling process.

Abstract

Tendinopathy is a clinical syndrome marked by persistent localized pain and tendon thickening, stemming from repetitive overuse-induced trauma. This musculoskeletal condition poses diagnostic and management challenges due to its chronic nature. Management entails a multifaceted approach, encompassing activity modification, pain control, and rehabilitative exercise. The pathophysiological shift from inflammation to degeneration highlights the need for changes in comprehensive management strategies in which platelet rich plasma (PRP) injections have gained growing interest with limited literature support for its use in clinical practice. This literature review was performed to inform clinicians about the properties, safety, and efficacy of PRP injections as an adjunctive therapy in chronic tendinopathies. A comprehensive review of 12 clinical trials, exploring the efficacy of PRP injections was performed. The Primary focus of this review investigated the trends in efficacy, including pain reduction and activity improvement, using various functional assessment. Overall, studies comparing PRP with various modalities show promise in reducing pain, improving function, and fostering tendon regeneration. Combining PRP with physical therapy often yields superior outcomes, urging further exploration of optimal PRP formulations, concentrations, injection intervals, and the role of ultrasound guidance. This comprehensive analysis of PRP injections showcases their potential as an alternative for chronic tendinopathies, emphasizing tissue regeneration and safety. Addressing current limitations and optimizing protocols through further research will enhance our understanding and utilization of PRP in tendinopathy treatment.

Keywords: Tendinopathies, Platelet Rich Plasma, Glucocorticoid, Epicondylitis, Achilles Tendinopathy

Introduction

Tendinopathy is a clinical syndrome characterized by persistent, localized pain and tendon thickening (Scott & Rees, 2022). This syndrome is mainly caused by repetitive overuse of the tendon that causes trauma and microtears to the tendon. Tendinopathies can occur in many locations including the upper and lower extremities. There are a variety of different treatment modalities used for the management of tendinopathies as the symptoms can be difficult to control. An overview of tendinopathies including the diagnosis, pathophysiology and management is reviewed below.

Tendinopathy Overview

Soft tissue injuries are a significant contributor to disability and healthcare expenses, with more than one million office visits annually in the United States (Cole et al., 2010). Tendinopathy, characterized by the degeneration of the collagen protein within tendons, is a prevalent musculoskeletal condition that manifests as abnormal tissue within structurally intact tendons (Scott & Rees, 2022). The chronic nature of tendinopathies, often persisting for more than three months, presents challenges in diagnosis and management (Scott & Purdam, 2021). Clinical manifestations typically include insidious onset of localized pain, exacerbated by new activities or increased intensity in regular actions. Tendinopathies can occur in both the upper and lower extremities with some of the most common locations being the rotator cuff, epicondylar, patellar and achilles tendons. Diagnosis relies primarily on history, physical examination, and, if necessary, imaging techniques such as magnetic resonance imaging or ultrasonography (Kane et al., 2019).

Pathophysiology and Management

Tendons, known for their unique combination of strength, flexibility, and elasticity, play a crucial role in bearing loads and maintaining tensile strength over extended periods. However, their slow rate of oxygen consumption contributes to delayed healing compared to skeletal muscle (Kane et al., 2019). The pathophysiology of tendinopathy involves chronic microscopic tears in hypovascular tendon tissue, leading to scar formation rather than normal vascular and inflammatory-driven healing (Cole et al., 2010). Collagen fibers within tendons undergo disrepair and angioblastic hyperplasia, contributing to observable changes in tendon thickness and fiber orientation on imaging (Scott & Purdam, 2021). Tendinopathy is now recognized as a degenerative process with a failed healing response, challenging the previously prevalent notion of inflammation-driven conditions (Kane et al., 2019).

Management of tendinopathies is typically chronic and involves a multifaceted approach, including activity modification, relative rest, pain control, rehabilitative exercise, and protection. Understanding that complete symptom resolution may take over six months is crucial for both clinicians and patients (Kane et al., 2019). Common treatments include rest, nonsteroidal anti-inflammatory medications (NSAIDs), and periodic local corticosteroid injections (Andres & Murrell, 2008). Rehabilitative exercise, focusing on returning to a pain-free range of motion and subsequently increasing strength, forms the cornerstone of tendinopathy treatment (Kane et al., 2019). Additional noninvasive treatments may be trialed in refractory tendinopathies which include cryotherapy, topical nitroglycerin, extracorporeal shock wave therapy, therapeutic ultrasound, dry needling, and blood-driven therapies, before committing to invasive surgical procedures.

Risk Factors

Gender plays a significant role in tendinopathy risk, with men more prone to lower extremity issues, particularly in the patellar and Achilles tendons, compared to females. Conversely, gender exhibits no discernible relationship with tendinopathy in epicondylar tendons. Extrinsic risk factors contributing to tendinopathies encompass training errors, unfavorable environmental conditions, inadequate equipment, and premature return to sports (Scott & Rees, 2022). As the understanding of tendinopathy evolves from inflammatory perspectives to degenerative processes, comprehensive management strategies and a deeper exploration of risk factors become crucial for effective treatment and prevention.

Platelet Rich Plasma Injections Overview

Platelet-rich plasma (PRP) stands as a revolutionary medical intervention, providing a simple, efficient, and minimally invasive method to harness the regenerative potential of autologous growth factors. Originating from whole blood extracted from the patient, this innovative solution is meticulously processed through centrifugation, resulting in a final formulation with a concentration of platelets exceeding baseline levels (Cole et al., 2010). A typical blood specimen comprises 93% red blood cells, 6% platelets, and 1% white blood cells, serving as the raw material for the creation of PRP solutions (Dhillon et al., 2012).

PRP injections represent a therapeutic approach involving the drawing of a small blood sample, subsequent concentration of platelets through centrifuge, and the targeted injection of the resulting PRP solution into specific areas of the body. Platelets are a vital blood component known for their crucial roles in blood clotting and wound healing, contain an arsenal of growth

factors and bioactive proteins capable of stimulating tissue repair and regeneration (Cole et al., 2010).

The underlying principle of PRP therapy is to enhance the body's intrinsic capacity to repair and regenerate damaged tissues, particularly in the context of tendinopathy. Following an injury that induces bleeding, platelets become activated, aggregating to release granules laden with growth factors. These growth factors, characterized by diverse functions, collectively instigate an inflammatory cascade and healing process, fostering tissue regeneration. Two integral modulators, platelet-derived growth factor (PDGF) and transforming growth factor-B1 (TGF-B1), play key roles. PDGF functions in the initial stages of wound healing, enhancing the capacity to stimulate fibroblast proliferation and TGF-B1 increases the production of collagen fibers from fibroblasts, contributing to the healing process (Cole et al., 2010). Through this mechanism, PRP injections offer a promising avenue for accelerating the natural healing response, presenting a potential therapeutic effect for individuals suffering from tendon tissue degeneration. The multifaceted capabilities of PRP showcases its role as a therapeutic solution with the capacity to accelerate tissue and wound healing, marking a significant stride in the realm of regenerative medicine (Cole et al., 2010).

In recent years, PRP injections have emerged as a promising biological treatment for chronic tendinopathies, particularly in cases resistant to conventional interventions. This literature review delves into the extensive research conducted to understand the efficacy, properties, and mechanisms of action underlying PRP therapy. A comprehensive analysis compares PRP injections with various treatment modalities, including physical therapy rehab, sham injections, dry needling, and glucocorticoid injections, focusing on chronic tendinopathies affecting the elbow and Achilles tendons.

Research Question

When compared to other treatment modalities for chronic tendinopathies, are platelet rich plasma injections efficacious in pain management and tissue regeneration of chronic Achilles and Epicondylar tendons?

Methods

This literature review included an initial search within the Pub Med database using the mesh terms “platelet rich plasma (PRP)”, and “tendinopathies”. A further breakdown was conducted to include only human clinical trials and randomized controlled trials conducted within the last ten years. 58 studies were recovered for review. An additional search within the database was used for background information. Inclusion and exclusion criteria were applied to include only studies that referred specifically to the achilles tendons and the epicondylar tendons. This narrowed the search to 12 trials reviewed and analyzed for this literature review.

Literature Review

Efficacy of PRP injections for pain management and functional improvement in epicondylar tendinopathies

In the study performed by Montalvan et al. (2015), two ultrasound guided platelet rich plasma (PRP) injections were compared against two saline injections to evaluate the efficacy of PRP to reduce pain in patients with new onset, less than 3 months, lateral epicondylitis (LE). This study was conducted to test the presumed knowledge that PRP injections work to stimulate repair mechanisms and promote tissue healing.

Fifty patients with new onset lateral epicondylitis between 35-65 years of age were randomly assigned to either receive the PRP or the saline treatment. Exclusion criteria for this study was a history of LE for greater than 3 months, glucocorticoid infiltrates seen on US, and inflammatory or autoimmune conditions. There was a total of 34 men and 16 women equally divided into each group. The mean age of participants in each treatment group was 47 years. The primary outcome of this study was to see an improvement in pain on the visual analog scale (VAS) from baseline to 6 months and long-term pain relief at 12 months (Montalvan et al., 2015).

The procedure performed during the study lasted roughly 45 mins. A 12 mL blood sample was taken from each subject to keep the patients blinded to which group they were assigned to. The blood sample was prepared resulting in a “1.6-fold enrichment of platelets compared with whole-blood content” (Montalvan et al., 2015). The procedure consisted of 2ml of 1% lidocaine injected subcutaneously to numb the area before the tendon injection with the treatment solutions of either 2 ml PRP or 2ml saline. This procedure was performed twice, once

at baseline and again 4 weeks later for each patient. Each patient was evaluated at baseline, then again at 1, 3, 6, and 12 months for efficacy of treatment. Efficacy was assessed using the VAS (score 0-10), Roles-Maudsley Score (RMS) (1-4), and pain on isometric contraction of the LE tendons. The VAS score at baseline was 6.8 in the PRP group and 7 in the saline control group. The baseline mean Roles-Maudsley score was 3.2 and 3.4 in the PRP and saline groups respectively. Every patient was positive for LE tendon pain on isometric contraction in both treatment groups. Three subjects from each group were lost to follow up. The primary outcome, VAS score, in both the PRP and saline group decreased significantly between two consecutive points showing a significant intragroup comparison. The mean VAS score observed at the 6-month time was 2.5 (standard deviation (SD) 0.9 to 4.1) and 2.1 (SD 0.5 to 3.7) in the PRP group and saline group respectively. A further decrease in the PRP group to a mean score of 1.6 (SD 0.1 to 3.1) and the saline group to a mean score of 1.8 (SD –0.3 to 3.9) was noted. Variations from baseline VAS were not significantly different between the two groups at 6 months or 12 months. The secondary outcomes did not reveal any statistically significant differences between the PRP treatment and the Saline control group (Montalvan et al., 2015).

Table 1

Data Trended overtime via Functional Assessment Scales

Mean Scores	**Baseline**	**1 mo**	**3 mo**	**6 mo**	**12 mo**
PRP VAS	6.8	5.8	3.6	2.5	1.7
Saline VAS	7	5.1	3.7	2.1	1.8
PRP RMS	3.3	3.2	3	2.6	2.3
Saline RMS	3.4	3.2	2.9	2.5	2.2

Note. The trend in Visual Analog Scores (VAS) and Roles Maudsley Scores (RMS) between Saline and PRP injections performed by Montalvan et al. (2015) from baseline to 12 months post injection.

Montalvan et al. (2015) concluded that two intratendinous injections of PRP is not more efficacious than 2 intratendinous injections of saline for the treatment of naïve lateral epicondylitis of recent development. The authors thought that this could be in part because their

patients were naïve compared to more chronic tendinopathies that are treatment resistant. Strengths noted in this study were the use of a placebo control and the patients were screened for adverse side effects at each visit. A common weakness noted in studies reviewing PRP use on tendinopathies is thought to be the low population size that the studies are performed on; however, due to high inclusion and exclusion criteria this is not noted as a weakness.

In the clinical trial performed by Suzuki et al. (2022), serial MRI images were taken 6 times over a 2-year period to evaluate the sequential changes of lateral epicondyle tendon recovery following treatment with PRP injections.

The population of patients was taken from Aiko Orthopedic Surgery Hospital from October 2016 to March 2019. Thirty patients were included in the study after inclusion and exclusion criteria were met. The population consisted of 25 males and 5 females with mean age of 54 years. The inclusion criteria for patients to receive PRP injections consisted of pain that had failed three conservative nonoperational treatments and had continuous symptoms for 6 months from the initial onset of pain. Exclusion criteria consisted of patients less than 18 years of age, patients that had received a local steroid injection within 6 weeks, completed physical therapy within 4 weeks, or had taken NSAIDs within 2 weeks. Elbow surgery and other inflammatory conditions like rheumatoid arthritis or gout were also used for exclusion. The primary outcome of this study was to assess tissue repair on MRI assessment. Additional primary outcomes included pain resolution using the VAS and the PRTEE score following a single PRP injection. The study's secondary outcome was to find links between MRI scores and the clinical assessment scores via the VAS and PRTEE scores (Suzuki et al., 2022).

Twenty ml of whole blood was collected from each patient. A 2-step centrifuge process was applied to obtain 2 ml of leukocyte rich PRP solution containing a 5-fold increase in platelet concentration compared to the whole blood collected. Each patient then received 1 ml of 1% lidocaine to numb the area of penetration. Two ml of the PRP solution was injected into the tendon using the peppering technique. This study was conducted with data collected at baseline, and at the monthly checkups of 1, 3, 6, 12, 18 and 24 months (about 2 years). MRI scoring was classified into 4 categories (0-3) with 0 being normal with complete homogeneous low intensity and 3 being severe with severe focal increase in the tendon signal. MRI was used as it is a reliable tool for objective evaluation (Suzuki et al., 2022).

The mean baseline MRI score was 2.30 (SD 0.75). The results found no significant difference in mean MRI scores from baseline to 1-month $p>0.05$. A significant difference in MRI scores were seen from baseline to 3, 6, 12, 18, and 24 months, with mean scores of 2.30, 1.77, 1.13, 0.73, 0.60 and 0.33 respectively and a p value of $p<0.001$. A single PRP injection leads to significant improvements by 3 months and continues over a long timeframe via MRI assessment. Significant improvements in the VAS and PRTEE scores occurred by 1 month from baseline, $p<0.001$. Baseline mean scores were as follows; VAS 72 and PRTEE 56. 1 month mean scores were VAS 48 and PRTEE 36. This significant improvement in clinical assessment continued over 1 year. There was no significant difference between the mean values at 12 months and at 18 or 24 months. The secondary outcome results showed a negative association between MRI scores and clinical assessment scores, p value: $p>0.01$ (Suzuki et al., 2022).

Table 2

Trends in Data overtime on Functional Assessment Scales

Mean scores	Baseline	1 mo	3 mo	6 mo	12 mo	24 mo
MRI Scores	2.30	1.97	1.77*	1.13*	0.73*	0.33*
VAS scores	72	48*	34*	28*	15*	11*
PRTEE scores	56	36*	26*	18*	8*	6*

Note: The trend in Visual Analog Scores (VAS), Patient Rated Tennis Elbow Evaluation (PRTEE) and Magnetic Resonance Imaging (MRI) scores for PRP injections performed by Suzuki et al., (2022). * Denotes statistically significant from baseline, $p<0.01$

The study's outcome shows early pain relief up to 12 months after a single injection of PRP solution and significant long-term improvement in MRI scores continued through 24 months. The results suggest that PRP treatment improves both tendon recovery and pain management, however there is a time lag between tissue repair and pain resolution (Suzuki et al., 2022). The strength of this study included routine follow-up, every 3 months up to 24 months post injection. Follow-up was not lost because the hospital covered the cost of the PRP treatment, MRI, and follow-up consults. This allowed for thorough completion of the study with significant data collection. As stated in the discussion, one weakness of the study is the fact that they did not have a control population to compare normal tendon recovery against due to the hospital not being able to cover the cost (Suzuki et al., 2022).

The clinical study initiated by Dallaudière et al. (2014) was a largely inclusive study researching the potential therapeutic effects of PRP injections under ultrasound guidance for patients suffering from persistent tendinopathy caused by tendon microtears or tendinosis. The study focused on a multitude of tendon locations including the epicondylar, achilles, patellar, and various other tendons. The tendons of interest relevant to my project include the epicondylar and achilles tendons.

The study was conducted on 393 patients, and various tendon locations. Exclusion criteria consisted of pregnancy, infections, previous corticosteroid injections and inflammatory/ immunodeficiency conditions. 250 patients, 146 men and 104 women, had tendinopathies of the epicondylar tendons and 54 patients had tendinopathy involving the achilles tendon. The mean age of participants was 45 years old (SD 12.4) with an average duration of symptoms lasting 6 months before administration of the PRP trials. The aim of this study was to “assess the efficacy and tolerance of intratendinous injection of PRP, with controlled platelet and leukocyte number, under US guidance to treat tendinosis and tendon tear in a large group of patients with clinical and US follow-up" (Dallaudière et al., 2014). Assessment tools used for data collection during the clinical trial included the quick DASH (Disability of the Arm, Shoulder, and Hand) scale for upper limbs, the Western Ontario and McMaster University Osteoarthritis index (WOMAC) scale for lower limbs and the visual analog scale (VAS) ranging from 0-10 for pain assessment of all limb tendinopathies. Color doppler ultrasound was used to score blood flow within the tendon at baseline and at 6 weeks post injection follow up. A score of 0 (absence) to 3 (important) was used to measure vascular activity.

Each procedure consisted of obtaining a 27 mL blood sample, which was centrifuged to obtain the final PRP product. The obtained PRP solution had a 3-fold increase in platelet concentration compared to that of whole blood. The physicians conducting the study controlled the PRP solution to contain a controlled platelet count at 900,000 mm and leukocyte count at 200 mm. Patients then received a 10 mL local anesthetic of lidocaine before being treated with 3 ml of PRP intratendinously. Assessments for PRP efficacy were performed at bassline, 6 weeks and up to 32 months post treatment. US assessment was only performed at baseline and 6 weeks post treatment (Dallaudière et al., 2014).

"Patient achieved a significant clinical improvement when comparing function tests at baseline and 6-week follow-up with $p<0.001$ (Dallaudière et al., 2014)." The mean quick DASH scores for lateral epicondylitis were as follows: baseline 37.9 (SD 9.3), 6 weeks 16.0 (SD 6.9), and long term follow up at 11.7 (SD 4) showing statistically significant improvement in scores, $p<0.001$. Medial epicondylitis showed comparable results with baseline at 40.5 (SD 7.8), 6 weeks at 13.4 (SD 2.6) and long term follow up at 11.3 (SD 3.2) and p value $p<0.001$). The mean WOMAC scores for Achilles tendinopathies were baseline at 36.6 (SD 20), 6 weeks at 12.6 (9.6) and long term follow up at 11.7 (SD 4) with a p value of $p<0.001$. The overall VAS scores for all tendons treated showed significant improvement in both short term and long term follow up with baseline value of 5.8 (SD 1.6), 6 weeks at 2.3 (SD 1.9) and long term follow up at 1.0 (SD 1.5) with a correlated p value of $p< 0.01$. Finally, the US evaluation of lateral and medial epicondylitis was both 7.5 at baseline with improvement in vascularity to 1.8 and 0.5 at 6 weeks respectively. The US evaluation for the achilles tendon was 7.5 at baseline with increase in vascularity to 2.9 at 6 weeks post treatment. PRP treatment was successful with 349 patients (88.8%) being satisfied with the long-term results obtain post PRP treatment.

The data collected from this study strongly suggests that the use of a single PRP injection allows for rapid healing of tendinopathies with good tolerance to treatment. During the clinical trial patients were asked to report any side effects at each visit. Very few patients reported side effects from the study with the only side effect being local pain post PRP injection in 9 patients. A limitation to the clinical trial is the absence of a control group to compare against. The study had a large population size with 393 total patients analyzed allowing for great data to be collected. The fact that the physicians controlled for platelet count and leukocyte count makes

the study more reliable and allows for reproducible results by having set PRP reference ranges (Dallaudière et al., 2014).

Efficacy of PRP injections versus corticosteroid injections for pain management and functional improvement in epicondylar tendinopathies

Krogh et al. (2013) performed a randomized, double-blind, controlled trial to compare the effectiveness of PRP and glucocorticoid steroids to reduce pain at the primary outcome of three months compared to normal saline injections. The trial was conducted on a population size of 60 patients randomly divided into three groups to receive an injection of PRP, saline or glucocorticoids. 165 patients were assessed for eligibility with 60 patients qualifying with similar characteristics based on inclusion criteria. Inclusion criteria included LE symptoms for greater than 3 months, point of tenderness on direct palpation, and definite sign of tendinopathy on color doppler US of at least a grade two. Exclusion criteria consisted of patients younger than 18 years of age, recent corticosteroid injection within 3 months, pervious tennis elbow surgery and inflammatory disease like RA. The secondary outcome of this study was to reduce vessel activity on color doppler US and decrease tendon thickness. The primary outcome was assessed by the pain section of the Patient Rated Tennis Elbow Evaluation (PRTEE) questionnaire which was scored from zero (no pain) to ten (worst pain imaginable). Tendon functionality was assessed via the functional section of the PRTEE questionnaire and via vessel activity and tendon thickness on color doppler US. This was graded on a scale of 0-4 based on the amount of vessel activity noted on US and thickness of the tendon. Grade zero shows no vessel activity in the region and grade four shows vessel activity in greater than 50% of the region.

Twenty-seven ml of whole blood was obtained from the 20 patients in the PRP sample group. The solution was then centrifuged to prepare a 3 ml solution containing an 8-fold increase in platelet concentration compared to the whole blood obtained. Once the PRP solution was prepared a peppering technique was applied to inject 3ml PRP solution into the tendon via 7 tendon perforations under US guidance. The control group received 3 ml of saline solution via the peppering technique with 7 tendon perforations under US guidance. The steroid group received 1 ml of triamcinolone plus 2 ml of lidocaine solution injected via one perforation under US guidance. Pain evaluation was performed via the PRTEE scale at baseline before treatment protocol and again at 1 month and 3 months post treatment. Doppler US for vessel activity and tendon thickness was performed at baseline and 3 months post treatment (Krogh et al., 2013).

Glucocorticoid injections showed a statistically significant reduction in pain at 1 month compared to PRP and saline injections, steroid vs PRP: p=0.003*, steroid vs saline: p= 0.011. However, no significant difference was noted between the 3 groups at the primary end point of 3 months, Steroid vs PRP: mean difference –1.1, p= 0.717, Steroid vs. saline: mean difference –3.8, p= 0.229, PRP vs. Saline: mean difference –2.7, p=0.395. Glucocorticoid injections did show a significant decrease in color doppler activity compared to PRP and Saline. Steroid vs PRP mean difference -2.6, p<0.0001 (SD -3.1 to -2.2), Steroid vs Saline mean difference –2.0, p<0.0001 (SD -2.5 to -1.6). Glucocorticoids also showed significant decrease in tendon thickness compared to PRP and Saline. (Steroid vs saline: p <0.001, Steroid vs PRP: p=0.002). It was noted in the study that between the 3 groups, PRP injections were reported to be more painful to receive than both glucocorticoid and saline injections with mean difference –3.0 and 2.0 respectively (Krogh et al., 2013).

Table 3

Trend in data overtime on Functional Assessment Scales

Mean scores	PRP mean	Saline mean	GC mean	PRP vs GC p-value	PRP vs Saline p-value	GC vs saline p-value
baseline	27.5	25.0	28.0	NA	NA	NA
1 mo	27	23.3	18.2	P<0.003*	P=0.703	P=0.011
3 mo	21.5	21.7	20.9	P=0.717	P=0.395	P=0.299
Tendon thickness Baseline	5.4	5.3	5.1	NA	NA	NA
Tendon thickness 3 mo	5.7	5.9	4.9	P<0.002*	P=0.044	P<0.001*

Notes: The trend in mean scores between Glucocorticoids, Saline and PRP injections performed by Krogh et al. (2013). * Denotes statistical significance, p<0.01

The study was originally conducted with a primary endpoint of 12 months; however, 44 participants dropped out after the 3-month period due to unsatisfactory results, altering the primary outcome to 3 months. The authors had concluded that since so many participants had left after the first 3-month trial, data can only be collected up to this point. It was reported that "the regeneration of tendon tissue is a process that probably lasts more than 3 months. This implies that if the treatment effect has a late onset, it would not have been recognized in this trial, which could have been the case for PRP" (Krogh et al., 2013). The study showed that glucocorticoid showed better short term pain reduction (1 month) compared to PRP and saline injections, although it did not have a significant effect on pain reduction come 3 months post injection. Glucocorticoids did however show significant signs of reduced vessel activity and tendon thickness compared to PRP and saline at 3 months (Krogh et al., 2013). One strength of this study is the fact that they used a normal saline as a control group to test the PRP and steroid injections against. One weakness of this study was the fact that they had to move their original primary end point from the calculated 12 months to 3 months due to the large dropout rate (Krogh et al., 2013).

A triple blinded clinical trial completed by Kamble et al. (2023), compared the short term and long-term efficacy of ultrasound guided PRP injections versus ultrasound guided glucocorticoid injections in patients with lateral epicondylitis that failed conversative treatment. Conservative treatment included avoiding detrimental activities, NSAID use, bracing and physiotherapy for at least 6 months. 84 individuals were assessed for participation in the clinical study. 16 were excluded based on the exclusion criteria. This consisted of professional athletes, pregnant women, patients with systemic disorders including but not limited to blood disorders, diabetes, rheumatoid arthritis, and cervical radiculopathy. 64 total participants were analyzed in the study with a mean age of 40 years.

The 64 participants were divided equally into the two treatment groups with 32 patients receiving PRP injections and 32 receiving GC injections. Thirty ml of blood was drawn from each patient to eliminate bias. Ultrasound technology was used to locate the elbow pathology to deliver the treatment to the source causing the elbow pain. The patients within the GC group were treated with 1ml of saline plus 1 ml of triamcinolone (GC) and the PRP group was treated with 3 ml of the PRP solution both under ultrasound guidance. The patients were analyzed at baseline, 2 weeks, 1 month, 3 months, 6 months, 1 year and 2 years post procedure. Treatment was evaluated using the VAS, DASH score, PRTEE score and hand grip strength. Two patients within each treatment group were lost to the 2 year follow up due to covid restrictions in place at the time of this study (Kamble et al., 2023).

The VAS, DASH and PRTEE scores at baseline within the PRP group were 7.75, 41.71 and 43.40 respectively. The same scores at baseline within the GC group were 8.62, 43.65 and 45.34 respectively. The scores 3 months post injection in the PRP group were as follows VAS 2.53, DASH 11.0, and PRTEE 10.81. The 3-month results within the GC group were VAS 2.06,

DASH 8.46 and PRTEE 8.71. These results support the statement that GC provides short term relief compared to PRP injections with statistically significant p values $p<0.05$ in all categories. The PRP results, however, showed significant improvement in the long-term setting of 2 years compared to GC with p values $p<0.05$. The long-term results were as follows VAS1.25, DASH 4.0, and PRTEE 3.96 in the PRP group. Whereas within the GC group the long-term results were VAS 3.68, DASH 7.43 and PRTEE 7.53. Hand grip strength showed significant improvement within both groups at the two-year mark compared to baseline, however, no significant difference between groups was noted. Treatment was noted as successful with 31 patients (96%) treated within the PRP group compared to 20 patients (62%) being treated within the GC group (Kamble et al., 2023).

These results suggest that both PRP and GCs injections significantly improved the functional outcomes in terms of VAS, DASH and PRTEE scores with PRP being superior to GC in the long term. No adverse effects such as infection or tendon rupture were reported in any patient during the clinical trial. A disadvantage of treatment with PRP compared to GC is that with the healing process taking 3 months or longer the benefits of PRP are not seen until a few months after treatment. The cost of PRP injections may also be a disadvantage. An advantage of this study compared to others is the use of US guidance to accurately inject the elbow pathology of question. A disadvantage of some newer studies like this one performed from 2019-2023 was the restrictions placed due to the covid pandemic which limited the sample size and accounted for loss of follow up within 4 patients (Kamble et al., 2023).

The degenerative nature in the pathology of chronic tendinopathies compared to the once believed inflammatory nature is causing clinicians and researchers to question the use of steroids for the treatment of epicondylitis. The randomized trial performed by Gupta et al. (2020), aimed

to compare the efficacy of PRP injections to steroid injections at a short term and long-term time frame for pain management and functional improvement in patients with lateral epicondylitis. 80 patients with diagnosed lateral epicondylitis unresponsive to conservative therapy for a minimum of 3 months were selected as participants in the study. Exclusion criteria included differential diagnosis for elbow pain or contributing systemic diseases. Participating patients' ages ranged from 18-55 years of age with a mean age of 40 years old. The patients were randomized into two groups with 40 patients in each treatment group. Patients were kept NSAID free for 2 weeks pre injection phase to obtain baseline scores and adequate whole blood content.

Twenty ml of whole venous blood was obtained from group A (PRP group) only. A 4.3-fold increase in platelet concentration was obtained in the PRP solution compared to the whole blood collected. A peppering technique was then used to penetrate and distribute 3 ml of PRP solution to the patients in group A. Group B received 40 mg triamcinolone injected using the peppering technique. Patients were then prescribed gentle range of motion and isotonic exercises to be started 1 week post procedure and continue to perform during the clinical trial. Data was obtained at a time period of baseline, 6 weeks, 3 months, and 1 year. Efficacy was assessed via the visual analog scale (VAS), DASH scores, MEPS and GSS scales (Gupta et al., 2020).

The primary outcome of this study was to see a decrease in VAS scores from pre to post procedure. The baseline VAS scores were 81.00 and 77.50 in the PRP group A and Steroid group B respectively. At 6 weeks an excellent improvement was seen on VAS scores in group B VAS=13.75 compared to group A VAS=44.5, with statistical significant of $p<0.001$. These results were reversed at both 3 months and 1 year follow up with greater improvements seen in group A versus group B. The VAS scores within group A were as follows 3 months 4.00 and 1 year 2.50. The VAS scores within group B were as follows at 3 months 22.75 and 1 year 13.50.

Likewise, data from the DASH, MEPS and GSS scores aligned with the data from the VAS scores were group B showed greater improvement at a short term of 6 week and the group A exhibited better results at 3 months and 1 year post procedure (Gupta et al., 2020).

"The effectiveness, in all aspects was observed to be more rapid in onset with CS injections, while PRP injections had a slower, yet more well sustained impact" (Gupta et al., 2020). A strength seen in this study compared to some similar studies is the use of the peppering technique, platelet concentrations between the optimal level of 500-1000x10^3, and the use of 4 different outcome measurements. A huge limitation to this study was the smaller sample size and that it was not controlled or blinded to the patients or physician (Gupta er al., 2020).

Efficacy of PRP versus other treatment modalities in epicondylar tendinopathies for pain management and functional improvement.

It is noted that needling of the LE tendons under local anesthetic has been an effective treatment for chronic LE. Therefore, clinicians are curious as to the effects that needling with PRP will contribute to treatment for chronic LE. Mishra et al. (2014), conducted a prospective clinical trial to evaluate the clinical effect of tendon needling with PRP versus the active control of tendon needling with bupivacaine for patients suffering with chronic lateral epicondylitis.

Three hundred and one patients were screened for participation in the clinical trial based on the inclusion criteria of elbow pain for greater than 3 months, pain unresponsive to at least 1 conservative treatment and pain on palpation of the lateral epicondyle. After exclusion criteria 230 participants were randomized to receive either the PRP (n=116) or active control (n=114). The trial was conducted over the course of 5 years from 2006 to 2011 with 12 centers involved. A total of 119 patients completed the full 6 months follow up. The mean age of participants was

48 years of age within the PRP group and 47 years of age in the active control group. The evaluation measures used to assess the efficacy of the treatment groups included the primary assessment via the Visual analog scale (VAS) and the secondary assessment via the PRTEE scale. Data was collected for each participant at baseline, 4, 8, 12 and 24 weeks (Mishra et al., 2014).

Approximately 30 ml of venous whole blood was collected from each participant to keep the patients blinded to which treatment group they were a part of. The GPS Biomet PRP production system was used at all 12 facilities to ensure similar end result PRP solutions. The Biomet system produced inactivated leukocyte rich PRP solution with platelet concentration 5x that of the whole blood collected. The patients within the PRP group received 3 ml of the PRP solution administered via the peppering technique with 5 tendon penetrations. The patients within the active control group received 3 ml of bupivacaine using the same peppering technique via 5 tendon penetrations (Mishra et al., 2014).

A long term clinically meaningful improvement was found in patients treated via needling with LR-PRP compared to patients treated via needling with bupivacaine. Patient outcomes were followed both at a short-term timeframe of 12 weeks and long-term time frame of 24 weeks. At 12 weeks the PRP treated patients reported an improvement of 55.5% mean VAS scores compared with 47.7% in the active control group ($p=0.163$). At 24 weeks, a statistically significant improvement in mean VAS scores ($p=0.019$) was seen in patients treated with PRP compared to those treated with the active control. Patients that received the PRP injection report a 71.5% improvement in their pain score on VAS compared to 56.1% improvement in pain on VAS seen in the active control group. However, there was no statistical difference between the PRP group and the active control group at any time frame using the PRTEE scale to determine

functional improvement of the LE tendon. The overall success rate, defined as 50% or greater reduction in pain, was clinically better in the PRP group with an 82.1% in pain reduction compared to 60.3% pain reduction in the active group and a p value of p=0.008 (Mishra et al., 2014).

No significant differences were found at 12 weeks, but at 24 weeks post treatment via needling with PRP was efficacious in pain reduction and overall improvement compared to those treated via needling with bupivacaine. This trial supports the hypothesis that PRP works to improve blood flow and tendon healing to ensure pain reduction in patients with chronic epicondylitis. The strength of this study includes the use of a similar active control, blinding of the participants and the multicenter approach. The multicenter approach also allowed for the reproducibility of results across multiple centers, which is essential for testing the effectiveness of a product like PRP. The authors of the study report that a standardized rehabilitation protocol would have also beneficial to the trial. As stated in the research article, further investigation into the potential mechanism of action is needed (Mishra et al., 2014).

Lim et al. (2018) states “PRP is promoted as an ideal autologous biological blood-derived product that can be exogenously applied to various tissues, where it releases high concentrations of platelet-derived growth factors that enhance wound, bone, and tendon healing.” In the research study performed, the biological components of PRP and clinical effects for treatment of lateral epicondylitis were investigated. Lim et al. (2018) conducted a controlled trial that compared the efficacy of a single PRP injection in addition to physical therapy compared to physical therapy alone for treatment of lateral epicondylitis.

One hundred and fifty-six patients that had the diagnosis of lateral epicondylitis on MRI that met the inclusion criteria of LE pain for greater than 3 months with no improvement despite

receiving conservative treatment were assessed for participation in the clinical study. A total of 120 participants were included in the clinical trial after exclusion criteria including systemic, hematologic and neurological diseases. A total of 105 participants completed the study to the end point of 24 weeks, with 55 patients within the PRP group and 50 patients in the PT group. Efficacy of treatment was assessed using the visual analog scale (VAS) for pain severity, Mayo elbow score (MAYO) for functional improvement and MRI assessment. The VAS and MAYO scores were assessed at baseline, 3 months, and 6 months. MRI assessment was performed at baseline and at 6 months. Pain relief via the VAS score was the primary outcome of this study (Lim et al., 2018).

Three 9 ml tubes of venous whole blood were collected from the participants within the PRP treatment group. A 5 ml leukocyte rich PRP solution was prepared with a platelet and WBC increase of 6x that of the whole blood obtained. The patients within the PRP group were treated with 2 ml of the PRP solution via ultrasound guided needle tenotomy into the tendon. The patients within the control group only received a physical therapy program without any sham injections. All patients were advised to use a tennis elbow strap and perform stretching and strengthening exercises during the 6 months trial period.

At 4-weeks post injection, the PRP group showed a statistically significant improvement in their VAS score by 40.6 points compared to the improved score by 29.9 points in the control group ($p<0.05$). Similar improvements were observed in the MAYO scores and MRI grades with statistically significant difference between the PRP treatment group and control group. The change in MAYO score improved by 16.23 points in the PRP group compared to an improvement by 8.42 in the control group. The MRI grades had improved by 1.11 in the PRP group and by 0.37 in the control group. All pain and function variables recorded via the VAS,

MAYO and MRI scores had significantly improved $p<0.05$ by 6 months post injection. Therefore, it was concluded that local injections of PRP in addition to physical therapy offer a better symptomatic relief and may produce a better treatment outcome compared to physical therapy alone (Lim et al., 2018).

The PRP solution was analyzed for the biological components that aid in tendon recovery. Concentration levels for platelet derived growth factors (PDGF), transforming growth factor-B (TGF-B), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and interleukin –1B (IL-1B) were obtained and investigated using the Pearson correlation coefficient for statistical correlation with the clinical scores. PDGF and TGF-B levels were significantly increased in the PRP solution compared to whole blood. "TGF-B level significantly correlated with MAYO clinic performance scores ($p=0.042$) and MRI grade improvement $p=0.05$. Thus TGF-B level in PRP is considered to play a pivotal role in tendon healing (Lim et al., 2018)."

After synthesizing the results, this clinical trial demonstrates that a single PRP injection in addition to physical therapy is more effective in pain reduction and improved function in chronic lateral epicondylitis. The concentration of transforming growth factors B may be the key component within PRP that aids in tissue regeneration. A strength noted in this study was the breakdown of the growth factor levels within the PRP solutions obtained. This study sets the stage for similar studies to be performed in the future that further analyze the biological components and mechanism of action of PRP to help create a more unified product (Lim et al., 2018).

Efficacy of PRP versus other treatment modalities in achilles tendinopathies for pain management and functional improvement

There are several treatment options available for tendinopathies, ranging from rehabilitation to injections and ending with surgery. The emergence of growth factor injections have become a hopeful steppingstone to regenerate damaged tendon tissue and delay or even prevent tendonitis surgeries. Filardo et al. (2014) conducted a study with the aim of determining the long-term therapeutic effects of repeated leukocyte rich PRP injects for the treatment of chronic, refractory achilles tendinopathy. 20 patients with unilateral and 7 patients with bilateral achilles tendonitis, total of 34 tendons, were included in this study. The mean age of the population was 45 years of age with a total of 22 men and 5 women. Inclusion criteria consisted of failure of conservative treatment for greater than 3 months.

One hundred- and fifty ml blood sample was taken from each patient and was used to prepare the PRP solution. The PRP solution obtained on average contained five times the number of platelets compared to whole blood and 1.2 times the leukocyte count compared to whole blood. Each tendon was treated with a 5 ml PRP injection three times at two-week intervals. A fanning technique, via multiple penetrations, was used to inject the PRP solution directly into the tendon. Methods used to evaluate the efficacy of PRP injections on the achilles tendon included the VISA-A, Blanzina, EQ-VAS and the Tegner scale. Scores were obtained at baseline, 2 months, 6 months and a minimum of 30 months to a maximum of 54 months. After the second injection, the participants were enrolled in a rehabilitation program for 12 weeks. No major side effects were recorded during the evaluation period and an overall long-term improvement was seen in the tendons with improvement in all evaluation methods (Filardo et al., 2014).

Improvement in the VISA-A scale was the primary outcome of this study. At baseline the VISA-A score was 49.9 and improved greatly in 2 months with a score of 62.9 and a long-term benefit seen with scores of 90.0. Comparable results were seen in the EQ-VAS with baseline at 68 and long-term scores at 83.0 p value $p<0.001$. Equivalent results were also recognized on the Blanzina and Tegner scales with a significant improvement viewed between every assessment with $p<0.005$ in both scales. “Moreover 89% of the patients returned to sport and 93% of the patients were satisfied and would repeat the treatment if needed (Filardo et al., 2014). The only correlation noted between patient characteristics and tendon healing was that patients with more severe and longer duration of symptoms before treatment had slower return to activity.

Overall, multiple intratendinosis injections of PRP produced substantial results in the treatment of recalcitrant achilles tendinopathies with stable improvements noted over a long term follow up. Filardo et al. (2014), believes that there were various mechanisms of action employed in their clinical trial that contributed to the success of the PRP injections including the dry needling application, the direct biological stimulus and the activation of circulation derived cells. Although not compared in this specific study, it is important to note the different PRP formulations, the number of injections performed and the method of administration as PRP is an “off the shelf” product whose characteristics can vary greatly. A limitation noted in this study is the deficiency to use a control group to compare against.

Overload injury is the most common cause of Achilles tendinopathies. Most treatment options included rest and rehabilitation to allow the tendon to recover and become stronger. Growth factors however are growing in popularity with their assumed ability to aid in tendon repair. Krogh et al. (2016) performed a randomized clinical trial to determine the efficacy of a

single PRP injection versus a single saline injection for the treatment of chronic Achilles tendinopathy.

Inclusion criteria for eligibility was based on clinical diagnosis of achilles pain for more than 6 months, a current painful achilles and tendon thickening noted on doppler US. 24 participants were included in the randomized controlled trial based on exclusion criteria which included individuals less than 18 years of age, previous GC injection within 6 months and known inflammatory conditions. The participants were randomly assigned to one of two groups, the active PRP group or the control saline group. Tendon thickening was recorded via US and blood flow activity was recorded on doppler US and graded on a scale of 0-4. The primary assessment was improvement on the VISA-A scale with secondary assessment including changes in color doppler activity and tendon thickness. The primary end point of the study was 12 months, however due to a large dropout rate noted after three months the primary endpoint was adjusted to 3 months (Krogh et al., 2016).

To keep the trial blinded to the participants 54 ml of venous blood was obtained from every patient. The treatment procedure was approximately 20 minutes from blood collection to treatment injection. All patients received a 10 ml lidocaine injection around the achilles tendon before the treatment injection. The treatment injections were injected using antiseptic peppering technique with 7 tendon perforations distributed evenly in the thickest part of the tendon. 12 patients in the saline group received 6ml of 0.9% saline. The 12 patients in the PRP group received 6 ml of PRP with a platelet concentration 8 times that of the obtained venous blood.

“At 3 months there was no statistically significant difference between the PRP and saline (Krogh et al., 2016).” The VISA-A scores within the PRP group were as follows baseline 31.7 and 3.4 at 3 months, showing a great intragroup improvement. The VISA-A scores within the

saline group were as follows baseline 37.1 and 4.8 at 3 months, also showing a great intragroup improvement. However, the between group p values was p=0.868 showing no statistically significant improvement between the PRP injection and saline injections (Krogh et al., 2016).

Overall, a single PRP injection is not more efficacious than a single saline injection in treatment for chronic achilles tendinopathies at an end point of 3 months. The researchers concluded that the reason so many participants had dropped out of the study was because they were not satisfied with the results of the treatment. This study algins with various other studies comparing PRP versus saline however, contraindicates other studies that compare PRP and GC or PRP alone which shows significant improvement. The researchers noted that the peritendon injection of lidocaine may interfere with the activation of PRP and could account for no significant difference noted between the two groups. They also state that tendon regeneration processes may last more than 3 months and that the effect of the PRP is delayed and in this study would not be able to evaluate the efficacy of the PRP (Krogh et al., 2016).

Kearney et al. (2021) conducted a multicenter clinical trial with the goal of comparing the efficacy of a single PRP injection, compared to a sham injection of subcutaneous dry needling to reduce pain and improve function within the achilles tendon. Chronic achilles tendonitis is characterized by tissue dysfunction resulting in pain, swelling and activity limitation. 512 patients from 24 different clinics were screened from 2016 to 2020 for participation in the clinical trial based on inclusion criteria. Inclusion criteria consisted of patients 18 years of age and older with chronic achilles pain for a minimum of 3 months and a confirmed diagnosis of tendinopathy via US or MRI. After exclusion criteria were met, 240 participants from 24 different centers took part in the clinical trial. Exclusion criteria included pregnancy and systemic conditions. The mean age of participants was 52 years of age, and the mean duration of

symptoms was 24 months. 121 patients were allocated to the PRP injection group, and 119 patients were allocated to the sham injection group. 221 patients completed the clinical trial to the 6-month end point.

The injection procedure lasted roughly 30 minutes from the time of phlebotomy to treatment injection. 9 ml of whole blood was drawn from every participant to keep them blinded to which treatment they were receiving. The Glo PRP system was used at each clinical location that was taking part in the clinical trial to produce similar PRP solutions. The PRP preparation included a 2-step centrifuge process to produce 3 ml of a leukocyte rich PRP solution. Every patient was pretreated with 5 ml of 2% lidocaine over the injection area. The patients receiving the PRP solution were injected with 3 ml of PRP using 5 tendon penetrations. The patients within the sham injection group received 1 dry subcutaneous needle inserted into the skin but not within the tendon itself to avoid any bleeding which may add therapeutic effect. The evaluation methods used to assess the efficacy of the PRP solution versus the sham injection were the Victorian institute of sport assessment- achilles score (VISA-A) and the Visual analog scale (VAS). The VISA-A evaluation was performed at baseline, 3 months and 6 months whereas the VAS was evaluated at baseline, 2 weeks, 3 months and 6 months (Kearney et al., 2021).

There was no significant difference noted from baseline to 3 or 6 months between the PRP and sham injection on the VISA-A scale with adjusted p values of $p=0.88$ at 3 months and $p=0.36$ at 6 months. The VISA-A baseline mean score was 37 and 33.2 in the PRP and sham injection groups respectively. Both scores improved in 3 months with the PRP mean score of 47.0 and the sham injection mean score of 44.2. This further improved to 54.5 in the PRP group and 53.4 in the sham injection group in 6 months. This suggests improvement in tendon health and recovery overtime. However, as stated above, a difference between groups was not noted.

Similar results were seen on the VAS scale with a 3-month p value of p=0.85 and a 6-month p value of p= 0.94 between the PRP and the sham injections group. The most common adverse effect was mild discomfort at the injection site, followed by swelling and bruising. A total of 82% of the participants in the PRP group and 61% in the sham injection group experienced discomfort post injection. This number decreased to less than 1% in both treatment groups in 6 months.

Table 4

Trend in data overtime on Functional Assessment Scales

	Baseline	3 mo	6 mo	P value
VISA-A PRP	37.6	47.0	54.4	3 mo p=0.88
VISA-A saline	33.2	44.2	53.4	6 mo p=0.36
VAS PRP	4.2	3.6	2.7	3 mo p=0.47
VAS saline	4.6	3.6	2.6	6 mo p=0.22

Notes: The trend in Visual Analog Scores (VAS) and Victorian Institue Sports Assessment for Achilles (VISA-A) between Saline and PRP injections performed by Kearney et al. (2021)

The data obtained from this clinical trial shows that a single PRP injection is not more efficacious than a sham subcutaneous dry needle injection for mid portion chronic achilles tendinopathy up to a 6-month time frame. There were several limitations to this study compared to the others including only midterm follow up of 6 months and the lack of ultrasound guidance for solution injection. Another limitation was the lack of known platelet or growth factor increase in the PRP solution compared to the whole blood obtained (Kearney et al., 2021).

The use of platelet rich plasma for a possible treatment for chronic tendinopathies, although unclear, is becoming more sought after due to its theoretical healing effects. Numerous studies have completed clinical trials to determine the efficacy of PRP injections with no clear answer of treatment algorithm or effectiveness. This study performed by Hanisch and Wedderkopp (2019) was conducted with the aim of not only determining the short-term and long-term effects of PRP use on chronic achilles tendinopathies (CAT) but to also establish a

treatment protocol by comparing leukocyte-rich PRP (LR-PRP) solutions to leukocyte-poor PRP (LP-PRP) solutions. From 2012 to 2015, 84 participants that had failed conservative therapies for chronic achilles tendinopathies and have suffered from symptoms for at least 6 months were selected for participation in the clinical trial. 15 patients had experienced bilateral tendinopathy for a total of 104 Achilles tendons treated with PRP solutions. 36 participants and 41 tendons were allocated to the LR-PRP group, and 48 participants and 61 tendons were allocated to the LP-PRP group. The mean age of participants was 52 years of age.

Fifty-four ml of venous blood was collected from the patients in the leukocyte rich PRP group. The blood was buffered with 6 ml of bicarbonate and then transferred to the Biomet's GPS III centrifuge machine. The blood was then spun for 15 minutes to produce 5-6 ml of the LR-PRP solution. The LR-PRP solution contained a platelet concentration increase of 9.4 times and a leukocyte concentration increase of 5 times the whole blood level. 15 ml of venous blood was drawn from patients in the leukocyte poor PRP group. The blood was then transferred to the Arthrex ACP centrifuge machine and spun for 5 mins. This produced 5 ml of LP-PRP solution with a platelet concentration increase of 2 times that of whole blood. The patients were then treated with 5 ml of their respective PRP solution under ultrasound guidance via 5 tendon penetration. Pain and tendon severity was assessed at baseline, short-term follow up of 2 months and long term follow up of 8 to 24 months. The evaluation methods used to assess efficacy of treatment included pain via the VAS scale during rest and activity, and tendon severity via the VISA-A scale. A minimal clinically important change (MCIC) was reported at a 30% decrease in VAS or a 30% increase in VISA-A suggesting effective treatment (Hanisch & Wedderkopp, 2019).

After reviewing the results no significant difference was viewed between patients treated with leukocyte rich PRP and leukocyte poor PRP with a difference in change on VISA-A of 3.8 and 0.9 on the VAS- activity scale. However, there was a tendency to see better results in the LR-PRP group. The leukocyte rich PRP baseline mean score on the VASA-A scale was 45.4 (SD 28.6-62.4) and increased to 56.5 (SD 30.2-82.8) by 2 months' timeframe. A similar increase was seen in the leukocyte poor PRP group with a VASA-A baseline mean score of 30.6 (SD25.5-35.5) and 2-month score of 44.7 (SD 37.9-50.8). A minimal clinically important change was noted for both the LR-PRP and LP-PRP group on the VAS- activity scale. The baseline mean score for LR-PRP was 7.3 (SD 6.7-7.9) which improved at 2 months to 3.4 (SD 2.5-4.4), with further improvement seen at a long-term follow-up of 1.8 (SD 1.0-2.6). In the LP-PRP group, the baseline mean score was 7.7 (SD 7.3-8.2) with improvements seen at 2 months of 4.8 (SD 4.0-5.6) and further improvements to 3.6 (2.3-4.8) at long-term follow-up. A total of 63% of patients had reached MCIC in CAT severity. Leukocyte rich PRP injections provided a 79% benefit at 2-month short term follow up and 75% long term benefit for patients. Leukocyte poor PRP provided a 73% benefit in the short term and 61% benefit in the long term follow up (Hanisch & Wedderkopp, 2019).

Table 5

Trend in data overtime on Functional Assessment Scales

	baseline	Short term	Long term
VISA-A LR-PRP	45.5	56.6	NA
VISA-A LP-PRP	30.6	44.7	NA
VAS activity LR-PRP	3.4	3.0	1.8
VAS activity LP-PRP	7.7	4.8	3.6

Notes: The trend in Visual Analog Scores (VAS) and Victorian Institue Sports Assessment for Achilles (VISA-A) between Leukocyte Rich and Leukocyte Poor PRP injections performed by Hanisch and Wedderkopp (2019).

PRP may be a promising treatment for chronic achilles tendinopathies as treatment with PRP yielded a higher probability of minimal clinically important change. In addition, there was no significant difference in achilles tendon improvement and pain reduction between patients treated with leukocyte rich or leukocyte poor PRP. A limitation to this study was the lack of randomization to treatment groups and lack of a control group. Further studies into PRP preparation and the number of PRP treatments should be completed. This study lays out a guide to follow and compare against, with easily replicated methods, allowing further testing to be completed in the future to further advance the clinical implication of PRP injections (Hanisch & Wedderkopp, 2019).

Discussion

Platelet rich plasma injections are a type of biological injection, in which research has been conducted to investigate the efficacy, properties, and mechanism of action of this treatment modality in tendinopathies. This literature review compared PRP injections against other treatment modalities including physical therapy, sham injections, dry needling, and glucocorticoid injections for the management of chronic tendinopathies. The literature analyzed within this literature review highlighted trends in efficacy, duration of effect, PRP preparations, tissue growth factors, and safety of the injections. In addition, limitations to the studies analyzed and future grounds for research were reviewed.

Eight of the twelve total studies analyzed focused on elbow tendinopathies with a total of 879 participants suffering from lateral or medial epicondylitis. Five of the twelve total studies focused on Achilles tendinopathies consisting of 429 total participants suffering from achilles tendinopathy. The only study that researched both elbow tendinopathy and achilles tendinopathy was Dallaudiere et al. (2014) as seen in Table 1 of Appendix A.

Functional Assessment Scales Considerations

PRP injections are thought to be an effective alternative treatment for chronic tendinopathies which are treatment resistant because of its presumed knowledge that PRP solutions work to stimulate repair mechanisms and promote tissue healing, rather than masking pain receptors. Pain reduction, functional improvement, and tissue repair were assessed utilizing various scales to analyze the efficacy of PRP injections for use in chronic tendinopathies. As listed in Table 2 in appendix A, the main assessment scales used to evaluate elbow tendonopathy severity included the Visual Analog Scale (VAS), Patient-Rated Tennis Elbow Evaluation (PRTEE) scale, and the Disability of the Arm, Shoulder and Hand (DASH) scale. The Victorian Insitute of Sports Assessment- Achilles was the main parameter used to evaluate Achilles tendonopathy severity. Both ultrasound (US) and Magnetic Resonance Imaging (MRI) were used to assess tendon thickness and blood flow activity within the elbow and achilles.

Due to the wide variety of different outcome scales and parameters used within the literature reviewed, the Visual Analog Scale (VAS) was the main parameter used to assess the efficacy of PRP injections for pain reduction. The VAS is a subjective pain rating scale that quantifies pain on a continuum by measuring the intensity and frequency of symptoms. Only the select studies that used this scale of measurement could be comparatively analyzed. Efficacy of the PRP injections to reduce severity of symptoms and improve functionality was evaluated using both the PRTEE and DASH scales. The PRTEE scale is a 15-item questionnaire designed to evaluate pain and disability in patients with elbow tendinopathies. The DASH scale is a 30-item questionnaire used to evaluate disability and severity of symptoms of the upper limbs. Only the studies that used these scales of measurement were able to be comparatively analyzed.

The VISA-A scale consists of 8 questions used to evaluate the severity of Achilles tendonopathies by quantifying pain and functional performance. The efficacy of PRP injections to improve tendon health was assessed using ultrasound and MRI to visualize tendon thickness and blood flow activity within the tendon.

Follow-up Considerations

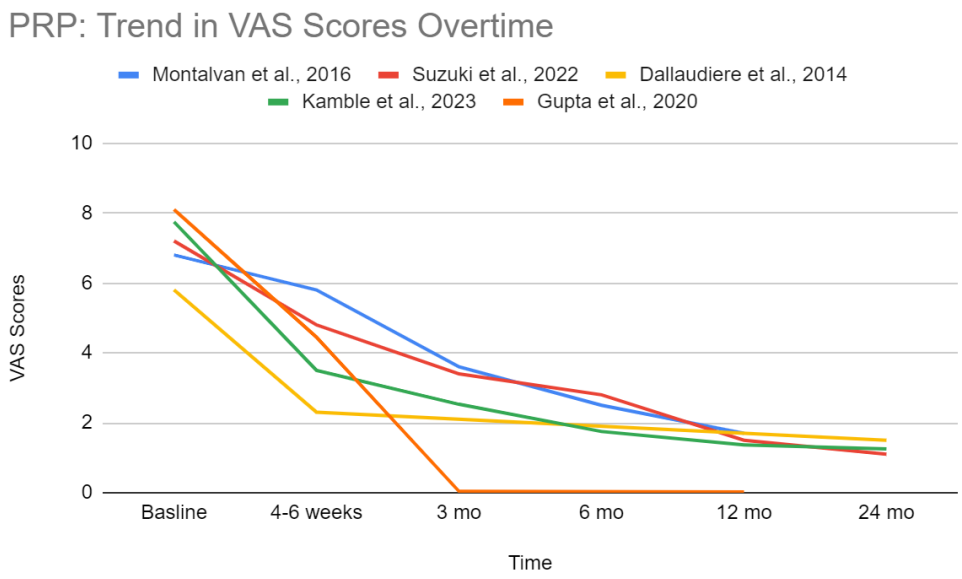
Table 1 of Appendix A summarizes the study design of the 12 studies analyzed with follow-up periods listed. As seen on the table, seven of the twelve studies had a follow up period greater than or equal to one year in length. Of those seven studies five had a follow-up period of 2 years or longer. There were two studies both performed by Krogh et al., that both had a primary end point of 12 months in which they experienced a large dropout rate at the follow-up period of 3 months altering their primary end point to 3 months. One of the studies was focused on elbow tendonitis and was completed in 2013, while the other study focused on achilles tendonitis and was completed in 2016. Krogh et al. (2013) and Krogh et al. (2016) were 2 of the 3 trials out of the 12 total trials that did not find PRP to be an effective alternate treatment for elbow or achilles tendonopathies.

Trends in Efficacy

The efficacy of PRP injections was assessed by observing improvements in pain, function and tendon regeneration as noted by the evaluation scales listed above. All the studies had shown improvements in the clinical symptoms of pain and function although not all the studies had seen significant improvements compared to a control group. Trends in improvement in pain, function and tendon thickness can be appreciated on Tables 3 through 6 in Appendix B.

Seven of the eight studies reviewing elbow tendinopathies used the visual analog scale for pain assessment. 5 studies using the visual analog scale were comparatively analyzed as appreciated on Figure 1 below. In the clinical trial performed by Mishra et al. (2014) the authors had reported a 71.5% improvement in pain by 24 weeks post injection compared to 56.1% improvement seen in the active control group. Dallaudiere et al. (2014) had noted that a significant decrease was observed between two consecutive visits throughout the 12-month study post PRP injection; however, there was no significant difference noted between the PRP and the control group at any point.

Figure 1

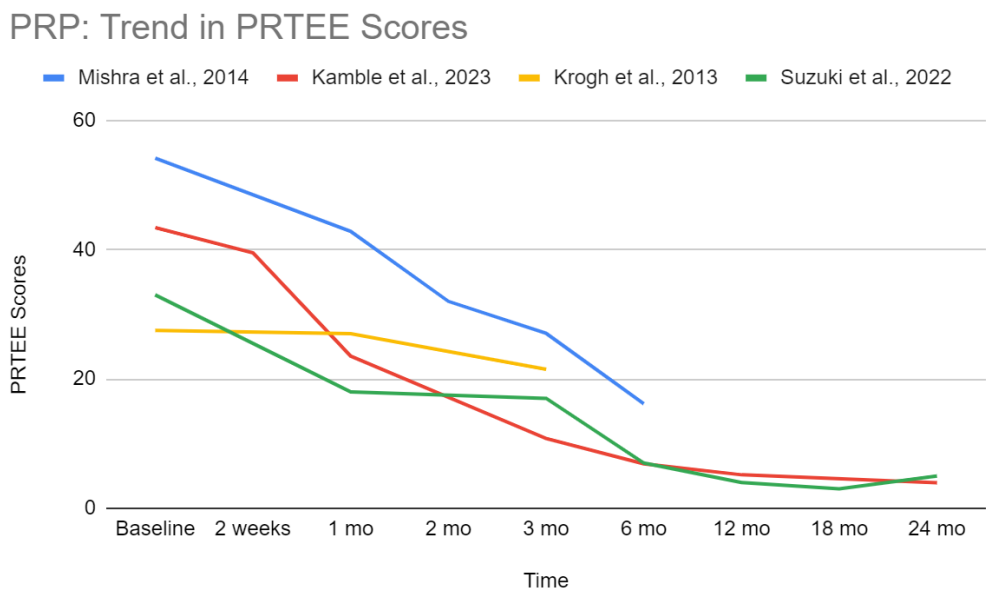


Notes: PRP injections showed significant improvement in elbow discomfort by 3 months on the Visual analog scale (VAS) that continued beyond 24 months which was noted in all 5 studies.

The main parameter used to assess the efficacy of PRP injection to improve elbow function was the patient-rated tennis elbow evaluation scale. There were four studies that were

comparatively analyzed as seen in figure 2 below. Mishra et al. (2014) noted that the PRP group reported more improvement over baseline on the PRTEE scale compared to control group, but these differences were not statistically significant. Kamble et al., (2023) stated that there was an improvement seen in patients treated with PRP and steroids; however, patients managed with PRP injections showed sustained improvement in functional outcomes at the long-term follow-up of 2 years. As seen on figure 2, PRP showed a major improvement in function by 3 months, that was sustained over a long-term period in all studies, besides the study performed by Krogh et al. (2013) in which results were only followed up to 3-month post injection.

Figure 2



Notes: PRP injections showed consistent improvement in elbow function by 3 months on the PRTEE scale that continued beyond 24 months. However, the study performed by Krogh et al., 2013 did not obtain similar results.

In this literature review, PRP injections showed a positive trend in overall treatment success as seen by improvement in pain, function and tendon pathology. Kamble et al., 2023 noted that treatment was successful in 31 patients in the PRP group accounting for 96%, out of which only 2 patients showed recurrence in symptoms six months post injection. Similar success was seen in the study performed by Mirsha et al., 2013 that observed a 60.1% success rate in the control group and an 82.1% success rate in the PRP group at 24 weeks post injection.

PRP versus Steroid injections for Efficacy

Three of the eight studies reviewing elbow tendinopathies analyzed the effects of PRP injections against the effects of corticosteroid injections. Krogh et al. (2013) performed a clinical trial that compared the effects of PRP injections and steroid injections to a control saline injection. They had concluded that an injection of PRP or steroid was not superior to a saline injection for improvement in pain after a three-month time frame. However, evidence showed that a steroid injection provided better short-term pain reduction at one month compared to PRP and saline injections, although it did not have a significant effect on pain reduction come three months post injection (Krogh et al., 2013). Similar long-term benefits after PRP injections were observed in the studies performed by both Kamble et al. (2023) and Gupta et al. (2020). Steroid injections and PRP injections both resulted in improvement in functional assessment scores used to evaluate pain reduction and improvement in hand grip strength. Steroid injections were noted to have a quick onset with max relief seen at one month post injection and last only a brief period. Whereas the PRP injections had a prolonged onset of action with little relief noted until three months post injection. A long-term gradual improvement post PRP injection was noted from three months' time to beyond the two-year follow-up timeframe (Kamble et al., 2023). In the trial performed by Gupta et al. (2020), steroid injections proved to have a rapid onset of

action with max benefit noted by six weeks, while PRP injection showed a slower onset on action with a more sustained impact over 12 months.

Both trials performed by Kamble et al. (2023) and Gupta et al. (2020) had a long-term follow-up period of 2 years and 1 year respectively, whereas the trial performed by Krogh et al. (2013) had a short-term follow-up period of 3 months. The trial conducted by Krogh et al. (2013) was initiated with a long-term follow-up period of 1 year, however by the 3 month follow up mark, 44 of the 60 participants had dropped out of the trial due to unsatisfactory results at this point in time. The authors had concluded that since so many participants had left after the first 3-month trial, data can only be collected up to this point. The authors had stated that the activation process of PRP could have a late onset greater than 3 months, in which improvements in pain and function would not be recognized within this trial (Krogh et al., 2013). This could contribute to the difference in efficacy observed between these 3 studies.

The analysis of these studies suggest that steroid injections have a quick onset and shorter duration of action as noted in numerous studies which had led to the search for an alternative treatment option. PRP injections although having a prolonged onset of action with very minimal changes noted until at least one month post injection, show promising long-term improvement in pain and tendon function as seen with follow-up periods beyond one year post injection.

PRP and PT rehab considerations

Lim et al. (2018) comparatively analyzed the effects of physical therapy in addition to PRP injections (PRP group) against the effects of physical therapy (PT group) alone. It was noted at four weeks post intervention, that the PRP group reported an improved score of 40.6 on the VAS compared to 29.2 in the PT group. Additionally improved scores were seen on the

MAYO scale at 16.23 in the PRP group compared to 8.42 in the control group. Finally, a 1.11 grade improvement on MRI assessment was seen within the PRP group compared to 0.37 grade improvement within the PT group (Lim et al., 2018). After a 24-week follow-up period, VAS (pain reduction), MAYO (functional improvement) and MRI grade (tissue repair) had significantly improved in the PRP + PT group compared to the PT group alone (Lim et al., 2018). Therefore, it was concluded that PRP injections in addition to physical therapy is considered to be a superior treatment for chronic elbow tendinopathies compared to physical therapy alone.

It should be noted that one additional study researching elbow tendinopathies performed by Gupta et al. (2020), had also mandated an exercise program with a set protocol, in addition to their treatment groups, that started one week post injection. The details of the exercise program, duration of the program, and relationship to the outcomes of the study were not described in the article reviewed. The result of the study found that PRP injections were more effective in reducing pain and improving function in elbow tendinopathies at the long-term follow up of 12 months compared to steroids, as noted via the VAS and DASH assessment scales (Gupta et al., 2020).

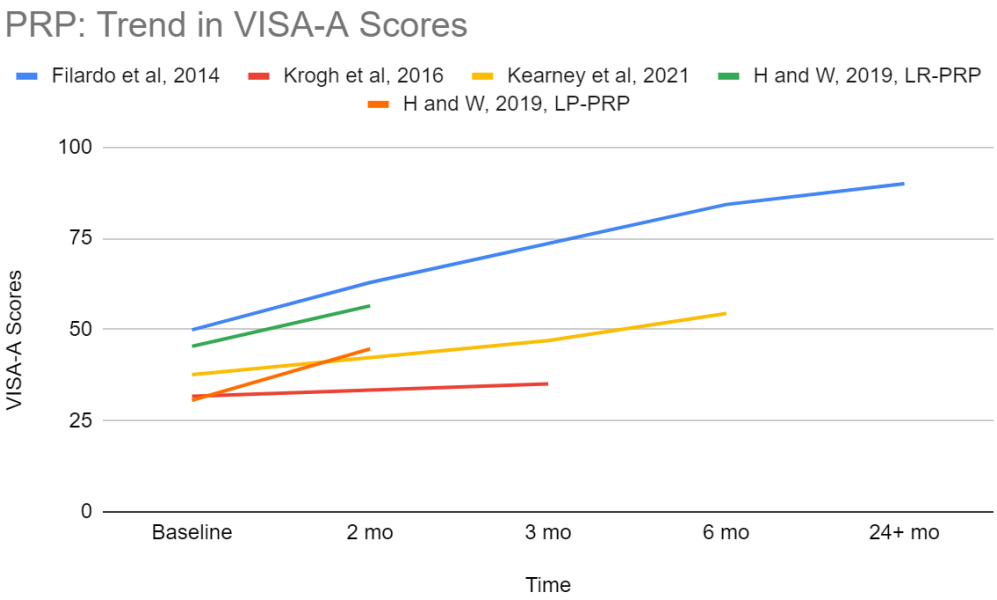
Two of the five studies reviewing Achilles tendinopathies used mandated physical therapy rehabilitation programs in addition to PRP injections during their clinical trials. These studies included Filardo et al. (2014) and Hanisch and Wedderkopp (2019). In the study conducted by Filardo et al. (2014), a 12-week rehabilitation exercise program was mandated to all participants to be started after the second PRP injection. They had noted that the rehabilitation protocol likely provided a contribution to symptom relief and functional improvement because an appropriate biomechanical stimulus after a biological treatment might increase the

regenerative potential of PRP and enhance tendon maturation synergically (Filardo et al., 2014). This study showed that repeated intratendinous injection of PRP with the addition of a mid-term rehabilitation program produced stable results over time with significant reduction in pain and improvement in symptoms. In the clinical trial performed by Hanisch and Wedderkopp (2019), all participants underwent an exercise therapy program starting 2 weeks post PRP injection. The details of the exercise program, duration of the program, and relationship to the outcomes of the study were not described in the article reviewed. However, the results obtained from this study were in alignment with additional studies reviewed by Hanisch and Wedderkopp (2019) that had concluded that physical therapy in addition to PRP injection may confer additional benefits. Through analysis of these studies, the addition of a physical therapy program to PRP injections tended to positively influence the clinical outcomes in both elbow and achilles tendinopathies.

PRP Effect on Achilles Tendinopathies

The efficacy of PRP injections for the treatment of achilles tendonitis was assessed by observing improvements in pain, function and tendon regeneration as noted by the VISA-A evaluation scale. Four studies that had used the VISA-A scale were comparatively analyzed. Kearney et al. (2021) observed that there was no significant difference noted from baseline to 3 or 6 months between the PRP and sham injection on the VISA-A scale. Filardo et al. (2014) noted that 89% of the patients treated with PRP injections returned to sporting activities and 93% were satisfied with their treatment results and would repeat the treatment. Hanisch and Wedderkopp (2019) concluded that PRP injections may be a promising treatment for chronic Achilles tendonitis when all other treatments have failed as noted by a 63% treatment success rate in patients. As seen in figure 3, PRP injections produced slow and steady improvement in VISA-A scores overtime.

Figure 3



Note: PRP injections produced slow but steady improvements in Achilles tendinopathies as seen on the VISA-A scale over 24 months.

The studies discussed contribute diverse perspectives on the efficacy of PRP injections for Achilles tendinopathy. While Filardo et al. and Hanisch & Wedderkopp suggest positive outcomes with PRP treatment, Krogh et al. and Kearney et al. raise questions about the short-term superiority and exclusive efficacy of PRP over alternative treatments. The variability in PRP formulations, injection techniques, and study methodologies emphasizes the need for further research to establish standardized protocols and address the complexities of Achilles tendinopathy treatment.

PRP preparation considerations

It is important to pay attention to the different PRP formulations, the number of injections performed and method of administration as PRP solutions are “off the shelf” products whose

characteristics can vary greatly. In the studies under review, there are a few key factors to consider in regard to PRP solutions, including the total amount of whole blood drawn, the type of PRP solution produced after centrifuge separation, and the final product volume to be administered. This data can be appreciated on Table 9 in appendix C. The total amount of whole blood volume obtained ranged from 9 ml to 150 ml. There was also a noteworthy difference in the final product volume produced ranging from 2-6 ml. There were no obvious trends noted based on the data values in regard to treatment efficacy.

Of the eight studies that researched elbow tendinopathies, four studies had produced a final PRP product that was leukocyte rich, and four studies had produced a final product that was leukocyte poor. Of the five studies that researched achilles tendinopathies, six different PRP solutions were created, with four being leukocyte rich and two being leukocyte poor. There was one clinical trial performed by Hanisch and Wedderkopp (2019) that directly researched the effectiveness of leukocyte rich PRP (LR-PRP) solutions to leukocyte poor PRP (LP-PRP) solutions in the treatment of achilles tendonitis. No significant difference was noted between patients treated with LR-PRP and LP-PRP at either a short-term or long-term follow-up period (Hanisch and Wedderkopp, 2019). Leukocyte rich PRP injections provided a 79% benefit in symptoms at a 2-month short term follow up and 75% long term benefit for patients. Leukocyte poor PRP provided a 73% benefit in symptoms in the short-term follow-up and 61% benefit in the long term (Hanisch and Wedderkopp, 2019).

Tissue Growths Factors considerations

Platelet rich plasma solutions are promoted as the ideal biological treatment as they are blood derived products that can be injected into various tissues (Lim et al., 2018). “PRP is thought to stimulate repair of the tendon via increasing the concentration of growth factors in the

local milleu, thereby helping in reversing the pathology responsible for the condition (Kamble et al., 2023).” Platelets contain over 300 bioactive cytokines and growth factors that aid in the coordination of tendon proliferation, differentiation and maturation (Mishra et al., 2014). Common growth factors noted within the PRP solutions used in the various research studies included platelet-derived growth factors (PDGF), transforming growth factor-B (TGF-B), Vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), fibroblast growth factor (FGF), Interleukin-1B (IL-1B) and insulin like growth factor 1 (ILGF-1).

The clinical trial performed by Lim et al. (2018) specifically researched the relationship between cytokine and growth factor levels and the clinical effect noted via assessment scales. The authors had measured the concentration levels for platelet derived growth factors (PDGF), transforming growth factor-B (TGF-B), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and interleukin –1B (IL-1B) to determine their statistical correlation to clinical scores. The authors had noted that PDGF-AB, PDGF-BB and TGF-B were the three growth factors that showed significant elevation in concentration levels within the PRP solution compared to the whole blood solution. “TGF-B level significantly correlated with MAYO clinic performance scores ($p=0.042$) and MRI grade improvement $p=0.05$. Thus TGF-B level in PRP is considered to play a pivotal role in tendon healing (Lim et al., 2018).” The authors had concluded that further research should be conducted to investigate the optimal growth factor release and number of platelets to optimize the effects of the PRP solutions. This data suggests that specific levels of certain growth factors like PDGF and TGF-B may further improve the efficacy of PRP injections.

Patient demographics considerations

Each research study analyzed had specific inclusion and exclusion criteria used to solidify the patient population that would undergo participation in their clinical trials. Some trends in the inclusion criteria noted included patients with chronic symptoms greater than 3 months, age greater than 18 years of age and failure of previous treatment options. Common trends in exclusion criteria consisted of systemic or autoimmune conditions like diabetes and rheumatoid arthritis, recent glucocorticoid injection within 6 weeks, recent elbow surgeries and pregnant individuals. Patients ranged in age from 18 to 60 years old, with a mean age ranging from 40-54 years old. Gender was only recorded in a handful of the research studies analyzed. All of the results recorded by Dallaudiere et al. (2014) were independent of age, gender, and type of tendinopathy (tendinosis or tear) at 6 weeks post injection. In the study conducted by Filardo et al. (2014), the authors had concluded that longer duration of symptoms before treatment was correlated with a slower clinical improvement and slower return to sport.

Safety

The safety of PRP solution has been a major concern in the consideration of PRP solutions as an alternate treatment option for tendinopathies due to its "off the shelf" design. It was initially thought to be a safer option in terms of significant adverse reactions than steroids due to its nature of being a naturally occurring substance within the body that is processed into a biological solution. The addition of anticoagulation and activation into the final PRP product was also questioned for safety in tendon use. Appendix D, Table 12, summarizes the reported adverse effects that occurred in each clinical trial. Of the twelve clinical trials analyzed, 5 studies had reported side effects including local post injection pain, swelling and bruising that last no more than 1 week. 3 of the 12 studies did not document any side effects at all. Additionally, no major

adverse effects like anaphylaxis or tendon rupture were reported. No major complication related to the injections or severe adverse events were observed during the treatment and follow up period, and an overall improvement in all the scores was recorded over time (Filardo et al., 2014).

Limitations

There were a handful of limitations noted by the research studies under review in the literature review, with the most common limitation being a small population size or lack of a control group. However, a small population size may not be seen as a limitation by professional statisticians when there is a strict inclusion and exclusion protocol. This is because the findings become for precise for a specific patient demographic. The lack of a control group is often normal in a study that is conducted over time as each person acts as their own control.

Additional limitations noted specifically for PRP injections include the cost and available facilities to obtain and perform the injection. PRP injections have an increased cost due to the equipment needed to produce the specific PRP solution. Another limitation that puts PRP injection at a disadvantage as a treatment option is the delayed mechanism of action and delay in pain and functional improvement. Kamble et al., 2023 noted that due to the process of tissue regeneration and healing being slow and taking around 3 months or more, the benefits of PRP are not evident in the short term (Kamble et al., 2023)

Grounds for future research

There are various avenues regarding PRP solutions in which future research would be beneficial. Initially future research to find the ideal PRP solution should be conducted that looks deeper into the type of PRP, leukocyte rich verse leukocyte poor, and optimal platelet

concentrations that would produce a premium solution. Additionally, more information on whether single verse multiple injections and the ideal time interval between treatments should be investigated. Finally, it was noted that ultrasound guidance should be included as part of future research as it enhances needle placement, and it is thought to improve treatment efficacy due to direct application of the PRP solution.

Conclusion

In conclusion, this scholarly project provides a comprehensive analysis of platelet-rich plasma (PRP) injections as a treatment modality for chronic tendinopathies, with a specific focus on elbow and Achilles tendinopathies. The literature review examined twelve studies, comparing PRP injections with various other treatment modalities, including physical therapy rehab, sham injections, dry needling, and glucocorticoid injections. The review delves into functional assessment scales, time considerations, trends in efficacy, and tissue regeneration.

The findings indicate a positive trend in the efficacy of PRP injections for pain reduction, functional improvement, and tendon regeneration in both elbow and Achilles tendinopathies. Notably, studies demonstrated significant reductions in pain over time, with sustained improvements in function observed. Success rates ranged from 60.1% to 96%, showcasing PRP's potential as a successful treatment option for chronic tendinopathies. The study designs varied, with follow-up periods ranging from three months to two years. Despite some studies reporting a significant decrease in pain and improved function with PRP injections, a few trials did not find PRP to be more effective than control groups, emphasizing the need for further investigation.

Comparisons with steroid injections reveal divergent onset patterns, with steroids providing rapid but short-term relief, while PRP exhibits a slower onset but prolonged

effectiveness beyond two years. Variances in study design and follow-up durations contribute to conflicting findings, emphasizing the need for nuanced analysis. The consideration of PRP in conjunction with physical therapy revealed that the combined approach often resulted in superior outcomes compared to physical therapy alone. The addition of a rehabilitation program positively influenced clinical outcomes in both elbow and Achilles tendinopathies.

The review also touched upon the importance of PRP preparation, including variations in formulations, leukocyte content, and growth factor concentrations. However, no significant conclusion could be drawn based upon the reviewed information. Future research should focus on refining PRP solutions, determining optimal platelet concentrations, investigating the impact of single versus multiple injections, exploring the ideal time interval between treatments, and incorporating ultrasound guidance for improved efficacy.

PRP injections show promise as an alternate treatment for chronic tendinopathies, with an emphasize seen in their potential tissue regeneration and safety. Further research is needed to address existing limitations, optimize treatment protocols, and enhance our understanding of the factors influencing treatment outcomes.

Applicability to Clinical Practice

Platelet Rich Plasma (PRP) injections have shown promise in the clinical treatment of chronic tendinopathy. The applicability of PRP injections in clinical practice for chronic tendinopathy treatment is supported by several factors including:

- **Regenerative Potential:** PRP contains a high concentration of platelets, which release growth factors like platelet-derived growth factor (PDGF) and transforming growth

factor-B1 (TGF-B1). These growth factors play a crucial role in tissue repair and regeneration.

- **Minimally Invasive:** PRP injections are a minimally invasive procedure, making them attractive for patients seeking alternatives to more invasive treatments like surgeries.
- **Autologous Source:** PRP is derived from the patient's own blood, reducing the risk of immune reactions or infections.
- **Targeted Treatment:** PRP injections can be precisely targeted to the affected tendon, providing a localized therapeutic effect.
- **Alternative to Conventional Treatments:** In cases where traditional treatments like rest, NSAIDs, and physical therapy have not yielded satisfactory results, PRP injections offer an alternative approach before turning to invasive measures.
- **Reduced Inflammation:** While tendinopathy was traditionally considered an inflammatory condition, recent understanding emphasizes degenerative processes. PRP, with its growth factors, may help modulate inflammation and promote healing in this context.
- **Clinical Studies and Evidence:** Research and literature reviews have explored the efficacy of PRP injections for chronic tendinopathy, often showing positive outcomes and improvements in pain and function compared to traditional treatments.

However, it's essential to note that while PRP shows promise, the evidence is not universally conclusive, and individual responses may vary. The selection of patients, proper administration, and consideration of specific tendons involved are crucial factors in determining the success of PRP therapy for chronic tendinopathy. Additionally, the PRP process can be more expensive and rarely covered by healthcare insurance which poses more challenges. Moreover,

ongoing research and clinical trials continue to contribute to our understanding of PRP's efficacy and its optimal role in the comprehensive management of chronic tendinopathy. As with any medical intervention, consultation with healthcare professionals is necessary to assess the suitability of PRP for individual cases

References

Andres, B. M., & Murrell, G. A. C. (2008). Treatment of tendinopathy: What works, what does not, and what is on the horizon. *Clinical Orthopaedics and Related Research*, *466*(7), 1539–1554. https://doi.org/10.1007/s11999-008-0260-1

Cole, B. J., Seroyer, S. T., Filardo, G., Bajaj, S., & Fortier, L. A. (2010). Platelet-Rich Plasma. *Sports Health*, *2*(3), 203–210. https://doi.org/10.1177/1941738110366385

Dallaudière, B., Pesquer, L., Meyer, P., Silvestre, A., Perozziello, A., Peuchant, A., Durieux, M. H. M., Loriaut, P., Hummel, V., Boyer, P., Schouman-Claeys, E., & Serfaty, J. M. (2014). Intratendinous Injection of Platelet-Rich Plasma under US Guidance to Treat Tendinopathy: A Long-Term Pilot Study. *Journal of Vascular and Interventional Radiology*, *25*(5), 717–723. https://doi.org/10.1016/j.jvir.2014.01.026

Dhillon, R. S., Schwarz, E. M., & Maloney, M. D. (2012). Platelet-rich plasma therapy—Future or trend? *Arthritis Research & Therapy*, *14*(4), 219. https://doi.org/10.1186/ar3914

Filardo, G., Kon, E., Di Matteo, B., Di Martino, A., Tesei, G., Pelotti, P., Cenacchi, A., & Marcacci, M. (2014). Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: Results at 4 years. *Blood Transfusion = Trasfusione Del Sangue*, *12*(4), 533–540. https://doi.org/10.2450/2014.0289-13

Gautam, V. K., Verma, S., Batra, S., Bhatnagar, N., & Arora, S. (2015). Platelet-rich plasma versus corticosteroid injection for recalcitrant lateral epicondylitis: Clinical and ultrasonographic evaluation. *Journal of Orthopaedic Surgery (Hong Kong)*, *23*(1), 1–5. https://doi.org/10.1177/230949901502300101

Gupta, P. K., Acharya, A., Khanna, V., Roy, S., Khillan, K., & Sambandam, S. N. (2020). PRP versus steroids in a deadlock for efficacy: Long-term stability versus short-term intensity-results from a randomised trial. *Musculoskeletal Surgery, 104*(3), 285–294. https://doi.org/10.1007/s12306-019-00619-w

Hanisch, K., & Wedderkopp, N. (2019). Platelet-rich plasma (PRP) treatment of noninsertional Achilles tendinopathy in a two-case series: No significant difference in effect between leukocyte-rich and leukocyte-poor PRP. *Orthopedic Research and Reviews*, *11*, 55–60. https://doi.org/10.2147/ORR.S187638

Hecht, M. (2018, November 8). *Tendinopathy: Definition, Comparison to Tendonitis, and Treatment*. Healthline. https://www.healthline.com/health/tendinopathy

Kane SF, Olewinski LH, Tamminga KS. Management of Chronic Tendon Injuries. Am Fam Physician. 2019 Aug 1;100(3):147-157. PMID: 31361101..

Kamble, P., Prabhu, R. M., Jogani, A., Mohanty, S. S., Panchal, S., & Dakhode, S. (2023). Is Ultrasound (US)-Guided Platelet-Rich Plasma Injection More Efficacious as a Treatment Modality for Lateral Elbow Tendinopathy Than US-Guided Steroid Injection?: A Prospective Triple-Blinded Study with Midterm Follow-up. *Clinics in Orthopedic Surgery*, *15*(3), 454–462. https://doi.org/10.4055/cios22128

Kearney, R. S., Ji, C., Warwick, J., Parsons, N., Brown, J., Harrison, P., Young, J., Costa, M. L., Collaborators, A. T., Dasari, K., Chapman, A., Carmont, M., Harrold, F., Mangwani, J., Loveday, D., Blundell, C., Chadwick, C., Townshend, D., Putchakayala, K., … Amiras, D. (2021). Effect of Platelet-Rich Plasma Injection vs Sham Injection on Tendon Dysfunction in Patients with Chronic Midportion Achilles Tendinopathy: A Randomized Clinical Trial. *JAMA*, *326*(2), 137–144. https://doi.org/10.1001/jama.2021.6986

Krogh, T. P., Ellingsen, T., Christensen, R., Jensen, P., & Fredberg, U. (2016). Ultrasound-Guided Injection Therapy of Achilles Tendinopathy with Platelet-Rich Plasma or Saline: A Randomized, Blinded, Placebo-Controlled Trial. *The American Journal of Sports Medicine*, *44*(8), 1990–1997. https://doi.org/10.1177/0363546516647958

Krogh, T. P., Fredberg, U., Stengaard-Pedersen, K., Christensen, R., Jensen, P., & Ellingsen, T. (2013). Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: A randomized, double-blind, placebo-controlled trial. *The American Journal of Sports Medicine*, *41*(3), 625–635. https://doi.org/10.1177/0363546512472975

Lim, W., Park, S. H., Kim, B., Kang, S. W., Lee, J. W., & Moon, Y. L. (2018). Relationship of cytokine levels and clinical effect on platelet-rich plasma-treated lateral epicondylitis. *Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society*, *36*(3), 913–920. https://doi.org/10.1002/jor.23714

Mishra, A. K., Skrepnik, N. V., Edwards, S. G., Jones, G. L., Sampson, S., Vermillion, D. A., Ramsey, M. L., Karli, D. C., & Rettig, A. C. (2014). Efficacy of platelet-rich plasma for chronic tennis elbow: A double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *The American Journal of Sports Medicine*, *42*(2), 463–471. https://doi.org/10.1177/0363546513494359

Montalvan, B., Le Goux, P., Klouche, S., Borgel, D., Hardy, P., & Breban, M. (2016). Inefficacy of ultrasound-guided local injections of autologous conditioned plasma for recent epicondylitis: Results of a double-blind placebo-controlled randomized clinical trial with one-year follow-up. *Rheumatology (Oxford, England)*, *55*(2), 279–285. https://doi.org/10.1093/rheumatology/kev326

Scott, A., & Purdam, C. (2021, June). *Overview of the management of overuse (persistent) tendinopathy—UpToDate*. https://www.uptodate.com/contents/overview-of-the-management-of-overuse-persistent-tendinopathy

Scott, A., & Rees, J. (2022, November 2). *Overview of overuse (persistent) tendinopathy—UpToDate*. https://www.uptodate.com/contents/overview-of-overuse-persistent-tendinopathy?search=overview%20of%20overuse%20(persistent)%20tendinopathy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Suzuki, T., Hayakawa, K., Nakane, T., & Fujita, N. (2022). Repeated magnetic resonance imaging at 6 follow-up visits over a 2-year period after platelet-rich plasma injection in patients with lateral epicondylitis. *Journal of Shoulder and Elbow Surgery*, *31*(8), 1581–1587. https://doi.org/10.1016/j.jse.2022.01.147

Appendix A

Table 1

Study Designs

Study Title	Year	Comparison	Level of Evidence	Location	Outcome	Follow up
Montalvan et al., 2016	2015	PRP Vs Saline	Blinded, controlled randomized trial	New Onset ET	Effective long term	12 months
Suzuki et al., 2022	2022	PRP alone	Case series	Chronic ET	Effective	24 months
Dallaudière et al., 2014	2014	PRP alone	Pilot study	Chronic ET and Chronic AT	Effective	>24 months
Krogh et al., 2013	2013	PRP vs Saline vs Steroid	Randomized controlled trial	Chronic ET	Not Effective	3 months
Kamble et al., 2023	2022	PRP vs Steroid	Prospective, blinded trial	Chronic ET	Effective long term	24 months
Gupta et al., 2020	2019	PRP vs Steroid +PT	Randomized trial	Chronic ET	Effective long term	12 months
Mishra et al., 2014	2014	PRP vs Bupivacaine needling +PT	Multicenter prospective clinical trial	Chronic ET	Effective	24 weeks
Lim et al., 2018	2018	PRP + PT vs PT alone	Prospective, randomized controlled trial	Chronic ET	Effective	6 months
Filardo et al., 2014	2014	PRP + PT	NA	Chronic AT	Effective	>24 months
Krogh et al., 2016	2016	PRP vs Saline	Randomized clinical trial	Chronic AT	Not Effective	3 months
Kearney et al., 2021	2021	PRP vs Dry needling	Multicenter clinical trial	Chronic AT	Not Effective	6 months
Hanisch and Wedderkopp, 2019	2019	LR-PRP vs LP-PRP + PT	Randomized controlled trial	Chronic AT	Effective	24 months

- LR-PRP: Leukocyte rich platelet rich plasma; LP-PRP: Leukocyte poor platelet rich plasma; ET: Elbow Tendinopathy; AT: Achilles Tendinopathy

Table 2:

Summary of Study Assessment Scales

Study Title	VAS	PRTEE	DASH	VISA-A	Others
Montalvan et al., 2016	X				RMS, Isometric Contraction
Suzuki et al., 2022	X	X			MRI Scores
Dallaudière et al., 2014 AT					WOMAC, US
Dallaudière et al., 2014 LE	X		X		US
Krogh et al., 2013		X			Doppler US
Kamble et al., 2023	X	X	X		Hand grip strength
Gupta et al., 2020	X		X		MEPS, GSS
Mishra et al., 2014	X	X			
Lim et al., 2018	X				Mayo Score, MRI score
Filardo et al., 2014				X	Blanzina, EQ-VAS, Tegner
Krogh et al., 2016				X	Doppler US
Kearney et al., 2021	X			X	
Hanisch and Wedderkopp, 2019	X			X	

- VAS: Visual Analog Scale; PRTEE: Patient-Rated Tennis Elbow Evaluation; DASH: Disability of the Arm, Shoulder and Hand; VISA-A: Victorian Institute of Sports Assessment-Achilles; RMS= Roles and Maudsley Scale; MRI: magnetic resonance imaging; WOMAC: Western Ontario and McMaster Universities Arthritis Index; US: Ultrasound; MEPS: Mayo Elbow Performance Score; GSS: Grip Strength Score

Appendix B

Table 3

Lateral Epicondylitis pain reduction via VAS Scores treated by PRP

Study Titles	Baseline	2 W	4 W	6 w	12 W	6 mo	12 mo	18 mo	24 mo	24+ mo
Montalvan et al., 2016	6.8		5.8		3.6	2.5	1.7			
Suzuki et al., 2022	7.2		4.8		3.4	2.8	1.5	1.4	1.1	
Dallaudiere et al., 2014	5.8			2.3						1.5
Krogh et al., 2013										
Kamble et al., 2023	7.75	5.37	3.5		2.53	1.75	1.37		1.25	
Gupta et al., 2020	8.1			4.45	0.04		0.02			

- VAS: Visual Analog Scale; W: weeks

Table 4

Lateral Epicondylitis Functional improvement via PRTEE Scores treated by PRP

PRP PRTEE score	Baseline	2 weeks	1 mo	2 mo	3 mo	6 mo	12 mo	24 mo
Mishra et al., 2014	54.15		42.83	32.01	27.05	16.17		
Kamble et al., 2023	43.4	39.5	23.53		10.81	6.87	5.18	3.96
Krogh et al., 2013	27.5		27		21.5			
Suzuki et al., 2022	33		18		17	7	4	5

- PRTEE: patient-rated tennis elbow evaluation

Table 5

PRP effect on tissue improvement via MRI or US

Study Titles	Baseline	6 weeks	3 mo	6mo	12 mo	24 mo
Suzuki et al., 2022 MRI Grades	2.30		1.77*	1.13*	0.73*	0.33*
Lim et al., 2018 MRI Grades	1.8		0.7*			
Krogh et al., 2013 US scores	LE: 5.4 mm		5.7 mm			
Dallaudière et al., 2014 ET US scores	LE: 7.5 ME: 7.5 mm	LE: 1.8* ME: 0.5* mm				
Dallaudière et al., 2014 AT US scores	AT: 7.5 mm	AT: 2.9* mm				
Krogh et al., 2016 AT US scores	9.9mm		10.4 mm			

- Mean MRI grade on a scale of 0-4 or US mean tendon thickness score in mm; ET= elbow tendinopathies; AT= Achilles tendinopathies. * Denotes statistically significant, $p<0.01$

Table 6

PRP efficacy via VISA-A scores for Achilles Tendons

Theme 4: VISA-A scores	Baseline	2 mo	3 mo	6 mo	24+ mo
Filardo et al., 2014	49.9	62.9		84.3	90
Krogh et al., 2016	31.7		35.1		
Kearney et al., 2021	37.6		47	54.4	
Hanisch and Wedderkopp, 2019 (LP-PRP)	45.4	56.5			
Hanisch and Wedderkopp, 2019 (LR-PRP)	30.6	44.7			

- Victorian Institute of Sports Assessment-Achilles

Appendix C

Table 7

PRP classification by Study

Study Title	Classification	Anticoagulation	Activation
Montalvan et al., 2016	Leukocyte Poor	None	None
Suzuki et al., 2022	Leukocyte Rich	None	None
Dallaudière et al., 2014	Leukocyte Rich	Acid Citrate Dextrose	None
Krogh et al., 2013	Leukocyte Poor	Sodium citrate	Sodium Bicarbonate
Kamble et al., 2023	Leukocyte Poor	Citrate Phosphate Dextrose	None
Gupta et al., 2020	Leukocyte Poor	None	None
Mishra et al., 2014	Leukocyte Rich	Acid Citrate Dextrose	Sodium Bicarbonate
Lim et al., 2018	Leukocyte Rich	Sodium Citrate	Calcium Chloride
Filardo et al., 2014	Leukocyte Rich	None	Calcium Chloride
Krogh et al., 2016	Leukocyte Poor	Sodium Citrate	Sodium Bicarbonate
Kearney et al., 2021	Leukocyte Rich	Sodium Citrate	None
Hanisch and Wedderkopp, 2019 (LP-PRP)	Leukocyte Poor	None	None
Hanisch and Wedderkopp, 2019 (LR-PRP)	Leukocyte Rich	Bicarbonate	None

Table 8

Study Specific PRP preparation

Study title	# of spins	Spin 1 (speed, mins)	Spin 2 (speed, mins)
Montalvan et al., 2016	1 spin	Unknown	
Suzuki et al., 2022	2 spins	600s, 10 mins	2000g, 10 mins
Dallaudière et al., 2014	1 spin	620g, 15 mins	
Krogh et al., 2013	1 spin	3200, 15 mins	
Kamble et al., 2023	2 spins	1800g, 15 mins	3500g, 10 mins
Gupta et al., 2020	2 spins	160g, 12 mins	460g, 18 mins
Mishra et al., 2014	1 spin	3200 rpm, 15 mins	
Lim et al., 2018	1 spin	1200 rpm, 6 mins	
Filardo et al., 2014	2 spins	1480 rpm, 6 mins	3400, 15 mins
Krogh et al., 2016	1 spin	3200 rpm, 15 mins	
Kearney et al., 2021	2 spins	1200 g, 5 mins	1200g, 10 mins
Hanisch and Wedderkopp, 2019 (LP-PRP), (LR-PRP)	1 spin, 1 spin	1400g, 5 mins 3200 rpm, 15 mins	

Table 9

Whole Blood Volume and Final PRP Product Volume

Study title	Blood volume collected	Final PRP product	Platelet enrichment	WBC enrichment	Leukocyte rich
Montalvan et al., 2016	12ml	2 ml	1.6x	NA	No
Suzuki et al., 2022	20 ml	2 ml	5x	Unknown	Yes
Dallaudière et al., 2014	27 ml	3 ml	3x	Unknown	Yes
Krogh et al., 2013	27 ml	3 ml	8x	NA	No
Kamble et al., 2023	30 ml	3 ml	Unknown	NA	No
Gupta et al., 2020	20 ml	3 ml	4.3x	NA	No
Mishra et al., 2014	30 ml	3 ml	5x	Unknown	Yes
Lim et al., 2018	27 ml via 3- 9 ml tubes	2 ml	6x	6x	Yes
Filardo et al., 2014	150 ml	5 ml	5x	1.2x	Yes
Krogh et al., 2016	54 ml	6 ml	8x	NA	No
Kearney et al., 2021	9 ml	3 ml	Unknown	Unknown	Yes
Hanisch and Wedderkopp, 2019 (LP-PRP)	15 ml	5 ml	2x	NA	No
Hanisch and Wedderkopp, 2019 (LR-PRP)	54 ml	5 ml	9.4x	5x	Yes

- ml: mililiter; x; times; NA: Not Applicable

Table 10

PRP dose cycle and time intervals

Dose, cycle and intervals				
Montalvan et al., 2016	Single penetration, US guided	2x	4 weeks	Arthrex: ACP
Suzuki et al., 2022	Single penetration	1x	NA	Cellrich: NIPRO
Dallaudière et al., 2014	Single penetration, US guided	1x	NA	Biomet's: Recover GPS II
Krogh et al., 2013	Peppering, US guided	1x	NA	NA
Kamble et al., 2023	US guided	1x	NA	NA
Gupta et al., 2020	Peppering	1x	NA	NA
Mishra et al., 2014	Peppering, 5 penetrations	1x	NA	GPS Biomet's
Lim et al., 2018	US guided	1x	NA	HUONS: kit
Filardo et al., 2014	peppering, multi penetration	3x	2 weeks	NA
Krogh et al., 2016	peppering, 7 penetrations	1x	NA	Biomet's: Recover GPS II
Kearney et al., 2021	5 penetrations	1x	NA	Glo PRP
Hanisch and Wedderkopp, 2019 (LP-PRP)	5 penetrations, US guided	1x	NA	Arthrex: ACP
Hanisch and Wedderkopp, 2019 (LR-PRP)	5 penetrations, US guided	1x	NA	Biomet's: Recover GPS III

Appendix D

Table 11

Study population and characteristics

Study Title	Total participants, Total tendons	PRP group	GC group	Control group	Mean age	Age Range	M:F ratio
Montalvan et al., 2016	50,50	25	NA	25	47	35-65	NA
Suzuki et al., 2022	30,30	30	NA	NA	54	18+	25:5
Dallaudière et al., 2014 AT	54,54	54	NA	NA	45		NA
Dallaudière et al., 2014 LE	250,250	250	NA	NA	45		146:104
Krogh et al., 2013	60,60	20	20	20	45	18+	29:31
Kamble et al., 2023	64,64	32	32	NA	40	20-60	29:35
Gupta et al., 2020	80,80	40	40	NA	40	18-55	
Mishra et al., 2014	225,230	112	NA	113	48		
Lim et al., 2018	120,120	61	NA	59			
Filardo et al., 2014	27, 34	27	NA	NA	45		
Krogh et al., 2016	24,24	12	NA	12		18+	
Kearney et al., 2021	240,240	121	NA	119	54	18+	
Hanisch and Wedderkopp, 2019	84, 104	LP-PRP= 36 LR-PRP= 48	NA	NA	52		

Table 12

Adverse effects related to PRP injection by Study

Study title		
Montalvan et al., 2016	Post injection site pain resolved within 72hrs Cutaneous allergic reaction after PRP injection	Affected 16% in PRP and 8% in the control group No cutaneous injections occurred with 2nd injection as prior local anesthesia and iodine was no longer used. No tendon ruptures occurred
Suzuki et al., 2022	No adverse reactions documented	NA
Dallaudière et al., 2014	Transitory local pain at site of injection No major side effects occurred	Affected 9 patients
Krogh et al., 2013	PRP caused increased post injection pain compared to saline and steroid No major sided effects occurred	The increased pain noted in the PRP injection was thought to be because of the PRP not the tendon penetrations.
Kamble et al., 2023	No major side effects occurred	NA
Gupta et al., 2020	No major side effects occurred in any patients	NA
Mishra et al., 2014	Severe elbow pain at injection site lasting 4 days No major side effects occurred	Affected 2 patients in the group
Lim et al., 2018	No adverse reactions documented	NA
Filardo et al., 2014	No major adverse reactions occurred at any time during treatment	NA
Krogh et al., 2016	No adverse effects occurred	NA
Kearney et al., 2021	Post injection site pain, swelling and bruising	Pain affected 97%, swelling seen 56%, and bruising occurred in 48%
Hanisch and Wedderkopp, 2019	No major side effects documented	NA